REMARKS

Claims 1-24 remain in this application. Claims 1-24 are rejected. Claims 25-36 are previously cancelled. Claims 1, 11-14, and 16 are amended herein to clarify the invention and are not considered to be narrowing but instead address matters of form regarding positively reciting the specific binding partners in claim 1, and grammatical matters in the other claims.

OBVIOUSNESS REJECTION UNDER 35 U.S.C. 103(a)

Claims 1-12 and 14-24 have been rejected under 35 U.S.C. 103(a) based on Yamashita in view of Peeters, and further in view of Oyama et al. Claim 13 has been rejected under 35 U.S.C. 103(a) based on the same combination of references yet further in view of Heller et al.

These rejections are traversed for the following reasons, which lead to the conclusion that considering Yamashita in combination with Peeters and Oyama et al. or further in combination with Heller et al., the presently claimed affinity sensor for detecting specific binding events in response to a sample medium would not have been obvious to one of ordinary skill in the art.

Yamashita Does Not Disclose An Affinity Sensor:

The Examiner has again erroneously referred to the Yamashita reference as teaching an affinity sensor at least nine times on pages 3-5 of the Office Action. In response to applicants' prior explanation that the Yamashita reference is not an affinity sensor, but rather a transistor controlled by gate structure on a protein with a Flavin molecule, the Examiner has responded in the Response to Arguments section as follows:

> In this case, Yamashita reference is definitely in the field of applicant's endeavor i.e., an affinity sensor with electrodes for detecting specific molecular binding events, wherein the immobilized specific binding partners covers the electrodes with a thickness which permits tunnel effects (Column 1, line 50 to Column 3, line 37 and claims 1 and 11). Therefore, the non-analogous art argument is not persuasive.

Applicants provide herewith an article "SURVEY AND SUMMARY From DNA biosensors to gene chips" Joseph Wang, Nucleic Acids Research, 2000, Vol. 28, No. 16, pgs 3011-3016, wherein on page 3011, in the second column an explanation of affinity sensors is given in the first column. As indicated, affinity sensors detect binding of a target analyte (the complementarily associated binding partner in claim 1) with a surface confined ligand partner (immobilized specific binding partner in claim 1). According to this description of an affinity sensor, the Yamashita reference is in no way an affinity sensor nor a

suggestion thereof for the reasons outlined below. Nowhere in the Yamashita reference is the word "affinity" or "biosensor."

Presently claim 1 of the present invention is directed to an affinity sensor having an area having immobilized specific binding partners for coupling complementarily associated binding partners. The binding of the complementary binding partner introduces the conductive particle into the system, which presence can be measured by means of the formation of a respective tunnel contact junction between the particle and the electrodes. The claim is thus directed toward the sensor prior to the formation of the tunnel contact junction. In other words, the claim is directed to a sensor that is not capable of conducting a current because affinity binding has not yet created a tunnel contact junction but is configured to permit formation of a tunnel junction upon binding. In order to permit such binding, the claim recites "said area being accessible to said complementarily associated binding partners provided in the sample medium."

In contrast, the Yamashita device is always capable of conducting a current, all that is needed is the application of a suitable potential on the electrodes. Application of complementary binding partners has no relevant meaning to the Yamashita device because the Yamashita device has a *gate covering proteins not for use in affinity binding*. First, the gate makes the underlying proteins unaccessible to binding partners in a medium. Second, the proteins are not for affinity binding.

Thus, Yamashita does not disclose an affinity sensor. Hence, the sensor in clam 1, is not the same as the transistor in Yamashita. The Yamashita transistor is not concerned with an area that has immobilized specific binding partners according to the present invention, as the transistor is already capable of single electron tunneling without further binding. In other words it is not capable of sensing the presence or absence of complementary binding partner (provided with one electrically conductive particle) that has affinity for the mentioned immobilized binding partner of claim 1. The Yamashita transistor will give a response irrespective of the presence or absence of the complementary binding partner provided a gate voltage is applied. It is the gate voltage that causes tunneling to occur, **not the binding of binding partners as in the presently claimed invention.**

The Examiner appears to suggest that the creation of the transistor of the Yamashita reference at some point produces a device which is an affinity sensor since the Examiner states that the area between electrodes of the Yamashita device corresponds to the area of claimed invention by stating:

> the area being adapted for receiving immobilized specific binding partners, the specific binding partners being capable of coupling complementarily associated binding partners directly or via further specific binding molecules, the area having a minimum width adapted for capture of at least one complementarily associated being partner provided with one electrically conductive particle within the area in such a way as to allow for formation of a respective tunnel contact junction between the particle and the electrodes (Abstract, Figure 1, Claims 1 and 11, and Column 1, line 50 to column 3, line 37).

This logic presumes that no gate is formed and some affinity binding takes place in the area between electrodes that produces a current, something which is in no way suggested or hinted at in the Yamashita reference. Binding does not provide for establishing tunneling in the Yamashita reference. Tunneling occurs in response to application of a gate voltage in the Yamashita reference. Claim 1 presently recites the following:

> said area being accessible to said complementarily associated binding partners provided in the sample medium and having a minimum width adapted for capture of at least one of said complementarily associated binding partners provided with one electrically conductive particle within said area by affinity binding with said immobilized specific binding partners to form a respective tunnel contact junction between the particle and the electrodes.

Yamashita does not describe an intermediate structure that could be considered to represent the sensor in claim 1. In column 4, Yamashita provides the method for preparing the transistor (lines 32-67). First a lipid bilayer is generated (lines 32-48), second a preparation is made containing the internal means of the transistor. This internal part contains the protein surface, the quantum dot, the intermediate electrodes and the control gate, respectively the α-helix protein, the flavin, the porphyrin and the polyacetylene (lines 49-58). Subsequently, the transistor is assembled by spraying and ultrasonic vibration followed by carbon vapor deposition to form the electric conductive layer (lines 59-67). All these steps are required to generate the transistor (see column 5, line 1). Thus, Yamashita describes

no intermediate that can be seen as an affinity sensor of claim 1 of the present invention.

The transistor in Yamashita can function in various ways. An electrical voltage can be applied to conductive surfaces 7 and 8 allowing the transfer of one electron (column 5, lines 12). The potential energy of the control gate can be influenced by applying an outer terminal (9) in contact with the control gate (the polyacetylene). In this way it is possible to obtain step-like current voltage characteristics. In none of these steps is an affinity of one molecule for another molecule is measured. The only response is to influences are the application of a voltage to the electrodes and the application of a voltage to the outer terminal. These influences cannot be interpreted as affinities of molecules for each other as this property is pure distribution of electrons which a subatomic part of molecules and not molecules by themselves.

Another reason why Yamashita does not disclose the present invention is the fact that the conductive particle (the control gate, the flavin molecule) is covalently bounded to the protein surface (the α-helix protein). The term "affinity," when used to describe the interaction between two molecules, refers to *non-covalent bonding* of the two molecules. In stark contrast, the Flavin molecule is *covalently* bonded to the protein in the Yamashita device. Thus, Yamashita does not disclose an affinity sensor of claim 1 of the present invention or an affinity sensor in any known meaning.

The Office Action presently appears to be applying the Yamashita reference alone to reject claim 1. It is respectfully submitted that for the numerous above cited reasons, the Yamashita reference cannot render claim 1 obvious.

The Cited Reference Fail to Provide Suggestion to Make the Proposed Combination:

The above shortcomings of the Yamashita reference are many. Each one of the shortcomings must be complemented by the combination reference in order for a claim to lack patentability in the basis of obviousness. It is not seen that Peeters provides any of the shortcomings of Yamashita.

Once again applicants further relate that the Peeters reference describes an affinity sensor, in stark contrast to the transistor of the Yamashita reference, consisting of ultra small atomic structures that can be arranged in clusters that serve specifically as molecular electrodes (column 4, line 19-32) or electronic protein receptors (column 4, line 37). Peeters provides a technology to build protein specific electronic receptors on a chip without the use of any biological binding agents, synthetic probes or complex micro-structures such as test wells. Peeters therefore teaches away from the present invention.

First off, Peeters is considered to be nonanalogous art to the Yamashita reference which is nonanalogous to the presently claimed invention. It is called to the

Examiner's attention that Peeters does not refer to Yamashita when he refers to technologies that are generally used for the detection of a single type or a few different types of molecules even though Yamashita issued nearly three years before Peeters. Whereas Peeters was quite thorough in his list of citations he did not include Yamashita as one. The reason for this is of course that Yamashita is not a technology for the affinity detection of a molecule, it is not an affinity sensor. The stimulus the transistor in Yamashita is responsive to is a difference in voltage not an affinity binding of molecules.

Again in the Response to Arguments section of the Office Action, the Examiner relies heavily upon the Oyama et al. teaching to claim there is motivation to combine the references. However, the Examiner is reminded that *the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant's disclosure. In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." MPEP §706.02(j) "Contents of a 35 U.S.C. §103 Rejection". It is respectfully submitted that the cited references fail to disclose a suggestion to make the proposed combination and the reasonable expectation of success required to establish a prima facie case of obviousness.

The Examiner states in the Response to Arguments the following:

> There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success.

However, as clearly noted above, the suggestion and expectation of success must be found in the prior art. It is not the applicants burden to shown an absence thereof, rather it is the Examiner's burden to point to the evidence of the prerequisites in the prior art itself. It is well settled that features of prior art references may not be assembled to establish obviousness using the pending claims as a template. Indeed, the court in *In re Fritch*, 23 USPQ 2d 1780, 1783–84 (Fed. Cir. 1992) stated the following:

> "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." (quoting *ACS Hosp. Systems, Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). . . . The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

Thus, the prior art reference must suggest some desirable attribute for making the proposed combination and not just provide an alternative. For the reasons submitted below, it is respectfully submitted that the references fail to provide the suggestions to modify the Yamashita reference and fail to establish any reasonable expectation of success in the making the proposed combination.

The Examiner provides the following rationale in the Response to Arguments section for suggesting the Oyama reference provides motivation for the proposed combination:

> Applicant also argues that there is no motivation to combine the references. This argument is not persuasive in view of the strong motivation provided by Oyama et al as Oyama et al. state, "J.C. Andle et al have reported the successful detection of DNA by the use of a sensor comprising a so-called SAW device having a comb electrode formed on the surface of a piezoelectric plate. In this report, the sensitivity of DNA detection is indicated to be 0.1 nanogram in mass sensitivity (Column 2, lines 26-31)." This argument is applicable to all other references.

It is respectfully submitted that the above reasoning totally inapplicable to the references because of the differences in modes of operation emphasized below. In particular, it is not seen how one would be motivated use *a comb structure which is taught by the art to be a resonator used to measure weight difference by detecting a frequency change in response to binding a molecule* in *a transistor device which operates in response to a gate voltage and provides no area for associated complementary pairs to bind.*

Oyama discloses a DNA sensor wherein DNA binding with a target molecule disposed on a resonating device, that is, a SAW device having a comb structure, reduces the mass of the target molecule and thereby alters a resonating frequency. The SAW device is used for establishing oscillations and the binding merely alters the frequency of the oscillations. This has absolutely nothing to do

with binding pairs enabling electron tunneling. Yamashita only effects tunneling when a gate voltage is applied. Nothing in the Oyama reference suggests that the combining of a binding pair would provide for tunneling. Also, nothing in the references would provide one with a reasonable expectation of success in building a sensor as claimed wherein the combination of the binding pair effects tunneling.

The passage referred to in Oyama (column 2, lines 26-32) is actually an interpretation of what is in the prior art of that patent. There is no mention of how this art must be interpreted in the context of the Oyama reference. The Examiner is kindly requested to indicate where in the passage referred to the reference to an affinity area is made.

Still further, it is submitted that contrary to the Examiner's broad assertion that the combination of Peeters and Yamashita is supported, it cannot be seen how elements from Peeters may be combined with Yamashita to arrive at the affinity sensor of claim 1 based upon the references. Peeters measures the presence or absence of binding of the protein itself. It does not utilize a conductive particle. Adding an electrode of Peeters to the transistor of Yamashita does not result in the biosensor of claim 1, as the electrodes in Yamashita do not provide any discrimination in the signal whereas they do so in the Peeters reference. It is not seen how the transistor in Yamashita can be modified to include the electrode of Peeters and thereby resulting claim 1 of the patent. The sensor of Peeters works in a

completely different way than the sensor of the present invention. Any combination of features in Peeters with Yamashita must fail. One of many reasons for this failure is that the control gate in Yamashita is always present. Without the gate the transistor does not function and thus cannot be used in any combination, whereas with it, the Yamashita reference is always conductive with a gate voltage applied and can therefore not function as a sensor of a binding event.

With respect to the so-called motivation to combine the Yamashita reference with the Peeters reference, the simple reference in Oyama to a citation wherein a comb structure is used on the surface of a piezoelectric plate is insufficient. At best it motivates a person skilled in the art to search for references using piezoelectric plates to measure DNA. Yamashita and Peeters do not use piezoelectric plates, thus the quote cited cannot be seen as a motivation to specifically combine Yamashita with Peeters. The mere reference to a comb structure is simply not sufficient as neither Peeters nor Yamashita refer to comb structure.

In the Response to Arguments section, the Examiner mysteriously makes the following statement:

> In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It appears that the Examiner has misunderstood the arguments presented or the significance of the citation applied, or both. Applicant is not *individually* attacking the references, but is instead attacking proposal to make the combination of references and examining the totally incongruent operation methods of the references. The Court in *In re Kelly* dealt with a situation where an expert opinion as to one reference was given and did not address the other references of the combination. The Court stated:

> Moreover, as set forth above, the test is not whether a suggestion to use digital timing in a cardiac pacer is found *in* Walsh (which was the test applied by Dr. Cywinski), but rather what Keller in view of Walsh and what Berkovits in view of Walsh would have suggested to one of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981);.

Thus, since it is clear that applicant has addressed the combination of references to show their incompatability, the Examiner's citation is irrelevant.

The Examiner further provides the following citation and statement with regard to applicant's assertion that the Yamashita reference is non-analogous:

> In response to applicant's argument that Yamashita is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See In re Oetiker, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Yamashita reference is definitely in the field of applicant's endeavor i.e., an affinity sensor with electrodes for detecting specific molecular binding events, wherein the immobilized specific binding partners covers the electrodes with a thickness which

> permits tunnel effects (Column 1, line 50 to Column 3, line 37 and claims 1 and 11). Therefore, the non-analogous art argument is not persuasive.

In view of the above in-depth explanation of the workings of the Yamashita device and the fact that it does not detect molecular binding events, which is the problem applicants seek to provide a solution to, it is respectfully submitted that the Examiner's application of the above citation is inappropriate. The Yamashita device is a transistor with a gate preventing detection of molecular binding events.

Finally, the Examiner states that "[t]here is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success" and provides the following citation:

> In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.).

The Examiner then submits the following:

> There is evidence in the Oyama reference of the enabling methodology, the suggestion to modify the prior art, and evidence that sensitivity of DNA detection was actually experimentally studied and found to be functional at 0.1 nanogram mass sensitivity level (Column 2, lines 26-31).

It is respectfully submitted that Examiner's contention that the Oyama reference provides an *enabling methodology* is clearly unsupportable in view of the above discussions. The Examiner has cited 5 lines of a reference referring to another reference which measures mass based on frequency change of a resonator. There is absolutely no methodology provided that would enable one to use the comb structure of a resonating device which indicates binding by a frequency change in a biotransistor device as disclosed in Yamashita which responds to a gate voltage, *not a mass change*, to effect tunneling and conduction, *not frequency change*.

Thus, it is respectfully submitted that the rejected claims are not obvious in view of the cited references for the reasons stated above. Reconsideration of the rejections of claims 1-24 and their allowance are respectfully requested.

Applicant respectfully requests a three month extension of time for responding to the Office Action. Please charge the fee of $475.00 for the extension of time to Deposit Account No. 10-1250.

In light of the foregoing, the application is now believed to be in proper form for allowance of all claims and notice to that effect is earnestly solicited. Please charge any deficiency or credit any overpayment to Deposit Account No. 10-1250.

Respectfully submitted,
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